PROFILING CONDITION-SPECIFIC, GENOME-WIDE REGULATION OF mRNA STABILITY IN YEAST

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The steady-state abundance of an mRNA is determined by the balance between transcription and decay. While regulation of transcription has been well studied both experimentally and computationally, regulation of transcript stability has received little attention. In this study, we took advantage of the fact that information about mRNA stability is implicitly represented in steady-state mRNA abundances. We developed a novel algorithm, MatrixREDUCE, that infers the position-specific affinity matrices (PSAMs) for unknown RNA-binding factors and their condition-specific activities, using only genomic sequence data and steady-state mRNA expression data as input. We identified and computationally characterized the binding sites for six mRNA stability regulators in Saccharomyces cerevisiae, which include two members of the Pumilio-homology domain (Puf) family of RNA-binding proteins, Puf3p and Puf4p.

We provide computational and experimental evidence that regulation of mRNA stability by the discovered factors is dynamic and responds to a variety of environmental stimuli. For example, little was previously known about the functional role of Puf3p, but our computation results suggest that Puf3p functions to destabilize mitochondrion-related transcripts when metabolite repressing sugars are present. We had previously shown that the COX17 3'-UTR is sufficient to direct Puf3p decay regulation when attached to the ORF of MFA2. Thus, to test the prediction of condition-specific regulation by Puf3p, a transformed strain expressing a MFA2/COX17 3'-UTR hybrid mRNA was grown in media containing either glucose (repressing) or ethanol (non-repressing) as the carbon source. A transcriptional shut-off was performed, and indeed, we found that the Puf3p-regulated MFA2/COX17 mRNA decays rapidly with a half-life of 2.5 minutes in the glucose media, but is stabilized ~4-fold in the ethanol media to a half-life of 10.5 minutes. The wild-type MFA2 mRNA control showed no change in stability between the two media conditions.

Our work suggests that regulation of mRNA stability is not a special case phenomenon, but rather a pervasive regulatory mechanism that rapidly adapts cellular processes to a changing environment. As long as transcript nucleotide sequence and steady-state microarray data are available, our computational methods allow one to discover the PSAMs of mRNA stability regulators, to determine which mRNAs are most likely targeted by the trans-factors, and to identify the conditions under which these factors modulate mRNA stability. Thus, dedicated methods for measuring genome-wide mRNA decay rates are not necessary for screening hundreds of conditions for dynamic regulation of mRNA stability.